REMARKS

Claims 1-74 remain in this application, with Claims 37-41, 73, and 74 withdrawn from consideration as directed to a non-elected invention. The Applicants request reconsideration and review of the application in view of the following remarks. The Applicants submit concurrently herewith a Notice of Appeal to permit the Examiner sufficient time to consider and respond to this communication.

Claims 1, 8, 10-36 and 42-72 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Erlander, et al. (WO 95/13369) in view of New England BioLabs catalog (page 11) (1993/1994 catalog) ("NEB"). Applicants respectfully request reconsideration and withdrawal of this rejection on the grounds that Erlander, et al. alone or in combination with NEB neither teaches nor suggests the presently claimed invention.

The presently claimed method differs from the method described in Erlander, et al. in at least two respects. First, the presently claimed method utilizes a set of 48 degenerate anchor primers to generate cDNA from the mRNA population. In contrast, Erlander, et al. discloses only a set of 12 anchor primers to generate cDNA from the mRNA population. The set of 48 degenerate anchor primers increases the likelihood that all mRNA transcripts in the population, including rare mRNA transcripts, will be reverse transcribed to cDNA. Moreover, using the set of 48 degenerate anchor primers (which end in the sequence –V-N-N), as opposed to the set of 12 degenerate anchor primers (which end in the sequence –V-N), greatly increases the likelihood that the anchor primer actually initiates synthesis at the precise point where the poly(A) tail joins the RNA. For example, the inventor has observed that anchor primers of the –V-N type have a high frequency of mispriming, presumably at an adenine-rich location upstream from the poly(A) tail.

Second, the presently claimed method generates a cDNA pool from cRNA using reverse transcriptase and non-phased 5' RT primers. See Claim 1 step (g). In contrast,

Erlander, et al. generates cDNA from cRNA using reverse transcriptase and one of 16 phased primers, i.e., primers whose 3'-terminus is –N-N, wherein N is one of the four deoxyribonucleotides A, C, G, or T. See Erlander, et al. page 24, line 29 to page 25, line 15. As shown in Example 3 of the present invention, the differences between using non-phased RT primers versus phased RT primers to generate cDNA from cRNA is notable. Specifically, Tables 1 and 2 of the present invention highlight the increased fidelity at the N_1 position after reverse transcription with phased RT primers (Table 1) or non-phased RT primers (Table 2). Fidelity was assessed by comparing the sequence match of a particular clone at the N_1 position to GenBank DNA sequences and tabulating occurrences of precise matches. In Table 1 (the method taught by Erlander, et al.), the fidelity at the N_1 position is essentially random (5 of 22 clones matched precisely), whereas all clones in Table 2 (the method of the present invention), including 5 clones from Table 1 that were incorrect at the N_1 position, matched precisely. No motivation or suggestion may be found in Erlander, et al. to use non-phased RT primers to generate cDNA from cRNA.

Moreover, the Examiner's contention that the present invention is obvious because Erlander, et al. suggests multiple rounds of PCR (Office Action, page 6, paragraph 3) does not address a fundamental difference between the present invention and Erlander, et al., i.e., the use of non-phased versus phased RT primers to generate cDNA from cRNA to increase fidelity at the N_1 position from essentially random to perfect. Any number of subsequent PCR steps using a cDNA template with incorrect sequence will not enhance the results of the method.

Accordingly, because Erlander, et al. does not teach or suggest the presently claimed method and because NEB does not cure this deficiency, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 1-4, 8, 10-36 and 42-72 are rejected under 35 U.S.C. § 103(a) as unpatentable over Erlander, et al. in view of NEB and further in view of Kato, et al. (EP 735 144 A1). As noted above, the combination of Erlander, et al. and NEB does not

teach or suggest the present invention. The addition of the Kato, et al. reference does not cure this deficiency. Kato, et al. teaches the ligation of biotinylated double-stranded cDNA adapters to double-stranded cDNA fragments produced by multiple digests with class IIs restriction enzymes. Applicants respectfully point out that the method of Erlander, et al., in addition to the differences noted above, lacks a step of ligation of double-stranded cDNA adapters to double-stranded cDNA fragments and does not suggest the addition of such a step. Furthermore, the method of the present invention does not teach or claim the step of ligation of double-stranded cDNA adapters to double-stranded cDNA fragments. Thus, there would be no motivation for one of skill in the art to combine the teachings of the references to arrive at the presently claimed invention.

Claims 1, 5-7, 8, 10-36 and 42-72 are rejected under 35 U.S.C. § 103(a) as unpatentable over Erlander, et al. in view of NEB and further in view of de Noronha, et al. (PCR methods APPL. (1992) 2:131-136). As noted above, the combination of Erlander, et al. and NEB does not teach or suggest the present invention. The addition of the de Noronha, et al. reference does not cure this deficiency.

Claims 1, 8-36 and 42-72 are rejected under 35 U.S.C. § 103(a) as unpatentable over Erlander, et al. in view of NEB and further in view of Ju, et al. (Anal. Biochem. (1995) 231:131-140). As noted above, the combination of Erlander, et al. and NEB does not teach or suggest the present invention. The addition of the Ju, et al. reference does not cure this deficiency.

In view of the foregoing, the Applicants respectfully submit that Claims 1-36 and 42-72 are in condition for allowance. Reconsideration and withdrawal of the rejections is respectfully requested, and a timely Notice of Allowability is solicited.

To the extent it would be helpful to placing this application in condition for allowance, the Applicants encourage the Examiner to contact the undersigned counsel and conduct a telephonic interview.

While the Applicants believe that no fees are due in connection with the filing of this paper, the Commissioner is authorized to charge any shortage in the fees, including extension of time fees, to Deposit Account No. 50-0639.

Respectfully submitted,

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